and unfavorable enthalpy, respectively. Furthermore, we characterize dock and lock states of the peptide based on the solvent accessible surface area. We observe that the Lennard-Jones energy of the system increases continuously in lock and dock states as the peptide dissociates. The electrostatic energy in the lock state increases as the peptide dissociates and inter-peptide hydrogen bonds are ruptured while it decreases in the dock state as new peptide-water hydrogen bonds are formed. We also observe that before unbinding from the fibril, the peptide has to overcome an enthalpic barrier of the order of 10 $kJmol^{-1}$. This barrier is associated to interactions between exposed phenylalanine residues of the fibril and the peptide. Implication of these results to fibril growth will be discussed.

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A Computational Study of Amyloid β-Protein Assembly in Crowded Environments

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Alzheimer's disease is strongly associated with aberrant amyloid β-protein (Aβ) assembly into heterogeneous, metastable oligomeric assemblies with structures that have not been experimentally characterized yet. The 40 and 42 amino acids long Aβ40 and Aβ42 are the two predominant Aβ alloforms in the brain. Whereas Aβ40 and Aβ42 oligomer formation from monomeric state is still inaccessible to fully atomistic explicit-solvent molecular dynamics, Aβ40 and Aβ42 oligomers were structurally characterized using discrete molecular dynamics (DMD) and an intermediate-resolution protein model within the DMD4B-HYDRA implicit solvent force field, and the corresponding oligomer size distributions well matched the available in vitro data. In vivo, however, Aβ coexists with other biomolecules in a rather crowded environment. To understand the effect of crowding on Aβ oligomer formation, we used the DMD4B-HYDRA force field and added to an ensemble of 32 monomeric Aβ40 or Aβ42 peptides inert spherical "crowders" with a diameter of 0.5 nm at various concentrations to examine their effect on Aβ40 and Aβ42 oligomerization pathways. Our results show that crowding shifts oligomer size distributions towards smaller oligomer sizes and increases solubility of both peptides in a concentration-dependent way. The effect is stronger for Aβ42, where crowding abolishes the multimodal character of the oligomer size distribution. Our structural analysis revealed that the stability of larger oligomers is compromised by effective osmotic pressure exerted by the crowders, resulting in an increased rate of assembly breakage. While in vivo crowding agents are not inert as the crowders in our study, we here reveal that crowding-induced osmotic pressure strongly affects protein assembly dynamics, which is of significance to the disease.

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Transition of Amyloid Oligomers to Mature Fibrils: Internal Conversion Vs. Competing Assembly Pathways?

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Deposition of protein plaques, rich in long rigid fibrils with a characteristic cross-beta sheet structure, is the pathological marker for human disorders ranging from Alzheimer's disease to type II diabetes and rheumatoid arthritis. Significant evidence has implicated the formation of globular oligomeric amyloids as the main pathogenic agent in amyloid diseases. At the same time, in vitro experiments indicate that amyloid oligomers and rigid fibrils are formed along distinct assembly pathways with characteristic growth kinetics. This raises the questions how these early-stage oligomeric intermediates are converted to the rigid fibrils dominating during the late-stages of most amyloid diseases?

We have investigated the transition from the formation of amyloid oligomers and their curvilinear polymers to the rigid late-stage fibrils using the model amyloid hen egg white lysozyme (hewL). We have shown that hewL oligomers form a distinct aggregate phase with a well-defined transition boundary. However these oligomers and their curvilinear fibrils are metastable against the formation of thermodynamically stable rigid fibrils. We therefore performed experiments to discern whether amyloid oligomer species were directly converted into the stable rigid fibril conformation or whether rigid fibril nucleation proceeded in parallel, i.e. in competition with, oligomer formation. To do so, we monitored the rates of rigid fibril nucleation right outside and inside the transition boundary for oligomer formation. Our data suggest that oligomer formation is in kinetic competition with rigid fibril nucleation for their monomeric growth substrate. Futhermore, we observed no signs that prior formation of oligomeric species accelerated the nucleation of rigid fibrils. The latter would be expected for conformational conversion of oligomers into rigid fibrils. If anything, prior formation of oligomers retards the nucleation of rigid fibrils.

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Structural Variations of Amyloid β-Protein Fibrils Seeded with Extracted Fibrils from Brain Tissue of Alzheimer's Disease Model Mice

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In our previous studies by electron microscopy (EM) and two dimensional infrared spectroscopy of amyloid fibrils prepared *in vitro* from synthetic 40-residue β-amyloid (Aβ40) peptides, it was shown that the Aβ40 fibril structure and its molecular structure are not uniquely determined by amino acid sequence. Instead, the fibril structure is dependent upon the growth conditions. The molecular structures of β-amyloid fibrils that develop in Alzheimer's disease (AD) are therefore uncertain. In this study, fibrils extracted from brain tissue of AD model mice (three strains of aged transgenic mice with increased levels of human amyloid proteins, 3xTg-AD, J20Tg-AD and 5xFAD) were used to seed the growth of synthetic Aβ40 fibrils. Because amyloid fibril structures propagate themselves *via* seeded growth, the structures of seeded Aβ40 fibrils likely reflect structures in AD brain. Negatively stained EM images indicate that seeded fibrils tend to appear twisted like a ribbon, with periodic narrowing or nodes. The distances between nodes (the "internodal" distances) were relatively homogeneous distributions (~145 nm) in the 3xTg-AD and J20Tg-AD mice. In 5xFAD, on the other hand, fibrils having short internodal distances (~30 nm) were observed in addition to the distributions (~145 nm) which were measured in two other strains of mice. The mass-per-length (MPL) evaluated from dark-field EM images indicates that the most prevalent numbers of filaments in fibrils are 3 and 4 but the dominant number of the filaments is dependent on the source of the fibril seeds. Overall, these results demonstrate that AD model mouse brain-derived fibrils have a distinct fibril structures, and the model most relevant to human AD has yet to be determined.

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Determination of Nucleation Mass for Amyloid-β Aggregation

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Protein misfolding and concomitant self-assembly towards ordered aggregates (amyloids) has emerged as an important event governing both functional and pathological events in cells. Both structurally and biophyiscally, amyloid formation is highly conserved involving the conversion of proteins (intrinsically disordered or globular) from their native monomeric states to well-organized, fibrillar aggregates in a nucleation-dependent manner. Although a plethora of literature exists on modeling such aggregations, the molecular mechanisms are poorly understood, especially those leading up to nucleation. In our study we use Aβ as the model system to test our theoretical framework for amyloid aggregation. Specifically, we focus on nucleation, which we believe to be a critical gate-keeping event which controls the dynamics of the entire pathway and determines the physiochemical and biochemical fate of the aggregates formed. In this study we clarify the mechanics of aggregation leading to nucleation, and how fibril morphology depends on size and conformation of the nucleus. The pre-nucleation dynamics are modeled by ODE simulations based upon mass action kinetics and also supported by experimental data. An alternative, novel approach, based upon stability of the equilibria is utilized to identify the optimal nucleation mass range and properties associated with the nucleus.

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Morphology Selection through Geometric Frustration in Twisted Filament Bundles and Fibers

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Rope-like assemblies of twisted protein filaments constitute a common materials archetype appearing in a range of biological contexts from extracellular filament bundles to amyloid fibrils. Owing to the numerous distinctions in molecular structure and interactions underlying these diverse assemblies, a common framework to predict and classify the basic mechanisms of structure formation in twisted filament assemblies is still lacking. In this study, we exploit a recent and surprising connection between the assembly of self-twisting filaments and assembly on spherically-curved 2D surfaces to develop a universal theory of morphology selection in twisted fibers and bundles. This theory shows that the size and cross-sectional